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Acute exacerbation of interstitial pneumonia following surgical lung biopsy

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Summary
Study objectives: Surgical lung biopsy (SLB) plays an important role in the diagnosis of interstitial pneumonia, however, the occurrence of acute respiratory failure following SLB remains largely unreported. We evaluated the incidence, clinical features, therapy and prognosis of acute exacerbation of interstitial pneumonia following SLB.
Design: Retrospective study of consecutive patients who underwent SLB to establish a diagnosis of diffuse lung disease between May 1989 and April 2000. Patients with an acute exacerbation following lung biopsy were studied, and the HRCT images of the chest before and after surgery were reviewed.
Measurements and results: Among the 236 consecutive patients with interstitial pneumonia who underwent a surgical lung biopsy, five (2.1%) (IPF, 3; NSIP, 1; COP, 1) developed acute exacerbation of the diffuse lung disease in the course of 1–18 days after SLB. The extent of parenchymal involvement on HRCT before surgery was

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not significantly different between operated and contralateral nonoperated lung. Significantly increased regions of parenchymal involvement on HRCT were seen postoperatively compared with the preoperative CT in both the operated ($20.7 \pm 12.5\%$ versus $38.2 \pm 10.8\%$, $P = 0.0431$) and nonoperated lung ($22.7 \pm 13.8\%$ versus $70.5 \pm 24.4\%$, $P = 0.0431$), but the extent of the parenchymal involvement was significantly greater on the nonoperated side ($P = 0.0251$). Two of the 3 IPF patients died from the acute exacerbation.

Conclusions: It is important to be aware of the possibility of acute exacerbation of interstitial pneumonia following SLB even after an apparently uneventful immediate postoperative course. The asymmetric image findings suggest that intraoperative respiratory management is a possible etiologic factor.

Introduction

Surgical lung biopsy (SLB) plays an important role in the diagnosis of interstitial pneumonia.[1] Although it is considered to be a relatively safe surgical procedure, the mortality from SLB has been reported to range between 0% and 12%[2] including patients in whom respiratory failure occurred following SLB.[3,4] Nishiyama et al.[4] reported the case history of a patient with idiopathic pulmonary fibrosis (IPF) who deteriorated after SLB. Utz et al.[3] reported that 2 IPF/UIP patients died within 30 days of biopsy because of acute pulmonary edema or acute respiratory distress syndrome (ARDS) among their patients with UIP; we suspect that acute exacerbation occurred postoperatively in these patients. However the occurrence of acute respiratory failure following SLB remains largely unreported.

In contrast with acute exacerbation following SLB, ARDS following pulmonary resection for lung cancer has long been known.[3–9] The recent report of Padley et al.[10] demonstrated by the use of CT values that ARDS following lung resection was asymmetric, occurring mainly in the nonoperated lung. This led us to the hypothesis that acute exacerbation following SLB, which is less invasive than pulmonary resection for lung cancer, could occur mainly in the nonoperated lung.

Recently, we have encountered several patients with interstitial lung disease who suffered acute exacerbation following SLB. Herein, we report the incidence, clinical features, therapy and prognosis. We also evaluated asymmetry of acute exacerbation by the use of chest CT.

Methods

Of 236 consecutive patients who underwent surgical lung biopsy (99 = open; 137 = thoracoscopic) to help establish a diagnosis of diffuse lung disease at Tosei General Hospital, Nagoya University Hospital, Toyohashi City Hospital, Kariya General Hospital, Komaki City Hospital, and Handa City Hospital between May 1989 and April 2000, five patients presented with an acute exacerbation following lung biopsy. By October 2002, all SLB specimens were reviewed by 2 pathologists (T.Y., M.K.) according to the currently redefined criteria for idiopathic interstitial pneumonias.[1] A retrospective investigation was undertaken of case histories, anesthesiology records, and image findings. Cases with clear postoperative complications, such as pneumonia, heart failure, hemothorax or pulmonary hemorrhage were excluded. One of the five cases was previously reported.[4] This study was approved by our institutional review boards, and informed consent was obtained from the patients or the next of kin.

All patients had examination of thin-slice CT of the chest before and after surgery, the latter during the acute exacerbation. The CT scans comprised 2.0-mm collimation sections, reconstructed with the use of a high-spatial-frequency algorithm. The CT scans were performed with a variety of scanners. None of the patients received intravenous contrast medium.

The CT images were reviewed independently by two observers (Y.K., T.J.) according to the method of Ichikado et al.[11] These observers did not know any of the patients' clinical information. The lungs were divided into three zones (upper, middle, and lower); each zone was evaluated separately. Each of the three zones corresponded to approximately one-third of the images from the lung apex to 1 cm below the domes of the diaphragm. In each patient, corresponding zones of CT were selected before and after surgery.

The observers assessed the extent of total parenchymal involvement independently for each of the three zones of each lung. The total parenchymal involvement meant areas with various findings including ground-glass attenuation, consolidation,

intralobular reticular opacities, interlobular septal thickening, and honeycombing, The CT score in the upper, middle, and lower lung zones was determined visually and was estimated to the nearest 10% of parenchymal involvement. Overall percentage of involvement was obtained by averaging the six lung zones. The final total parenchymal involvement was obtained by averaging the scores of the two observers.

Statistical examination

The interobserver variation of the extent of parenchymal involvement was evaluated with the Spearman's rank correlation coefficient, and the differences were evaluated by Bland-Altman plots.[12] Wilcoxon test and repeated measures two-ways analysis of variance were used to evaluate trends of parenchymal involvement on CT. A *P* value of less than 0.05 was considered to indicate a statistically significant difference.

Results

Clinical features of acute exacerbation

The incidence of postoperative exacerbation was 2.1% (5/236 patients). The exacerbation occurred within 48 h in 2 patients and between 48 h and 18 days in 3 patients. Postoperative exacerbation occurred in 3 of 80 (3.8%) IPF patients, in 1 of 28 (3.8%) NSIP patients, and in 1 (9.1%) of 11 COP patients.

Table 1 shows clinical data of the five patients on admission. None of these patients had shown accelerated decline before SLB. Although the blood gas analysis and pulmonary function test findings of case 3 did not indicate significant impairment, we diagnosed this case as IPF based on radiological and pathologic findings.

Table 2 shows the times of surgical procedure, anesthesia and FiO_2 1.0, the interval between surgery and exacerbation, test findings at the time of exacerbation, and gas exchange findings for the five patients who experienced exacerbation. None of these patients had received blood transfusion or had other factors known to induce ARDS. BALF findings of 3 patients for the nonoperated lung at the time of exacerbation showed a significant increase in neutrophil fraction compared to the preoperative findings (Tables 1 and 2). Neither cultures of sputum, blood, BALF and urine for bacteria, viruses, mycobacteria, and fungi nor clinical features including serum titers against Mycoplasma, Legionella and viruses revealed any infectious events which could be responsible for the deterioration.

Table 1 Clinical Data on admission of the five patients who showed acute exacerbation after surgical lung biopsy.

	Case 1	Case 2	Case 3	Case 4	Case 5
Histologic diagnosis	UIP	UIP	UIP	NSIP	OP
Age (yr)	60	69	59	74	67
Sex	M	M	M	M	F
Duration of symptom (mo)	24	18	4	5	5.5
Smoking (Pack-years)	Current smoker (60)	Ex-smoker (150)	Current smoker (20)	Ex-smoker (53)	Nonsmoker (0)
WBC (μl)	7500	6000	6900	8900	7800
CRP (mg/dl)*	1.7	0.1	—	0.2	0.1
ANA	NEG	NEG	NEG	NEG	NEG
RF	NEG	NEG	NEG	POS	NEG
VC (% predicted)	75.4	49.8	91.9	59.8	91.5
DLco (% predicted)	57.1	47.1	117.0	35.5	91.0
PaO_2 (mmHg), on air	58.2	80.0	92.2	63.7	76.0
BALF					
Cell counts ($\times 10^4$/ml)	44.3	21.4	30.0	33.0	21.0
% Macrophages	78.0	96.0	86.0	26.2	30.0
% Neutrophils	14.7	1.0	0	6.1	0
% Lymphocytes	7.3	2.7	14.0	67.7	66.4
% Eosinophils	0	0.3	0	0	0

Definition of abbreviations: UIP = usual interstitial pneumonia, NSIP = nonspecific interstitial pneumonia, OP = organizing pneumonia, M = male, F = female, CRP = C-reactive protein, *normal range; less than 0.7 mg/dl, NEG = negative, POS = positive, ANA = anti-nuclear antibody, RF = rheumatoid factor, VC = vital capacity, BALF = broncho-alveolar lavage fluid.

Table 2 Surgical data, clinical data, and BALF findings at exacerbation.

	Case 1	Case 2	Case 3	Case 4	Case 5
Histologic diagnosis	UIP	UIP	UIP	NSIP	OP
Surgical time (m)	54	80	79	40	55
Anesthesia time (m)	185	195	131	180	190
FIO_2 1.0 time (m)	80	120	NA	40	170
Time from surgery until exacerbation (days)	6	14	1	18	2
WBC (μl)	9000	13,100	7100	9800	11,000
CRP (mg/dl)*	9.0	3.8	2.0	17.0	10.8
PaO_2 (mmHg)	58.2	80.0	92.2	63.7	56.0
FiO_2	0.6	1.0	0.4	0.8	1.0
PaO_2/FiO_2	99	233	189	63	137
BALF					
Cell counts ($\times 10^4$/ml)	19.1	8.8	NA	14.0	NA
% Macrophages	34.3	50.7	NA	39.3	NA
% Neutrophils	59.7	49.0	NA	35.7	NA
% Lymphocytes	1.0	0.3	NA	21.4	NA
% Eosinophils	5.0	0.0	NA	3.6	NA

Definition of abbreviations: CRP = C-reactive protein, NA = not available, BALF = broncho-alveolar lavage fluid, *normal range; less than 0.7 mg/dl.

Radiologic findings of acute exacerbation

There was good interobserver agreement for the extent of lung involvement on HRCT ($r = 0.956$; $P < 0.001$). Bland-Altman plots for the extent of parenchymal involvement showed good interobserver agreement (mean difference was −5.7 and the limits of agreement between two observers in each patient ranged from −13.6 to 11.6, which fell within the mean ± 1.96 SD). The extent of parenchymal involvement on HRCT before surgery was not significantly different between operated and nonoperated lung (20.7 ± 12.5% versus 22.7 ± 13.8%). HRCT at acute exacerbation after SLB revealed extensive shadows on the nonoperated lung in all patients, except 1 patient who showed increasing involvement in both lungs without predominance. Significantly increased regions of the parenchymal involvement on HRCT were seen postoperatively compared with the preoperatively CT in both the operated (20.7 ± 12.5% versus 38.2 ± 10.8%, $P = 0.0431$) and nonoperated lung (22.7 ± 13.8% versus 70.5 ± 24.4%, $P = 0.0431$), but the extent of the parenchymal involvement was significantly greater on the contralateral side ($P = 0.0251$) (Figs. 1(a–d) and 2).

Treatment and prognosis of acute exacerbation

The postoperative treatment is shown in Table 3. All patients were treated with broad-spectrum antibiotics and corticosteroids. Three received intravenous corticosteroid pulse therapy (methyl-prednisolone 1 g/day for three days) followed by a tapered dose, three received methyl-prednisolone 2 mg/kg/day for 2 weeks followed by a tapered dose which had been reported effective for the fibroproliferative phase of ARDS,[13] and one received both therapies. Immunosuppressants were introduced in three patients: cyclophosphamide in one and cyclosporine A in two. Two of the three IPF patients needed invasive mechanical ventilation. One patient died 1 month after surgical lung biopsy due to respiratory failure. Another patient improved from acute exacerbation but his respiratory failure progressed slowly, and finally died five months after SLB. Of the remaining three patients, one required invasive mechanical ventilation management and two required noninvasive positive pressure ventilation (NPPV). All three remain alive (mean follow up duration, 58.7 months; range, 38–76).

Discussion

The present study has demonstrated that post-biopsy exacerbation occurred in 2.1% of 236 consecutive patients undergoing surgical biopsy for diffuse lung disease. Acute exacerbation occurred from immediately following surgery to 2–3 weeks postoperatively. It is noteworthy that exacerbation can occur 2–3 weeks postoperatively

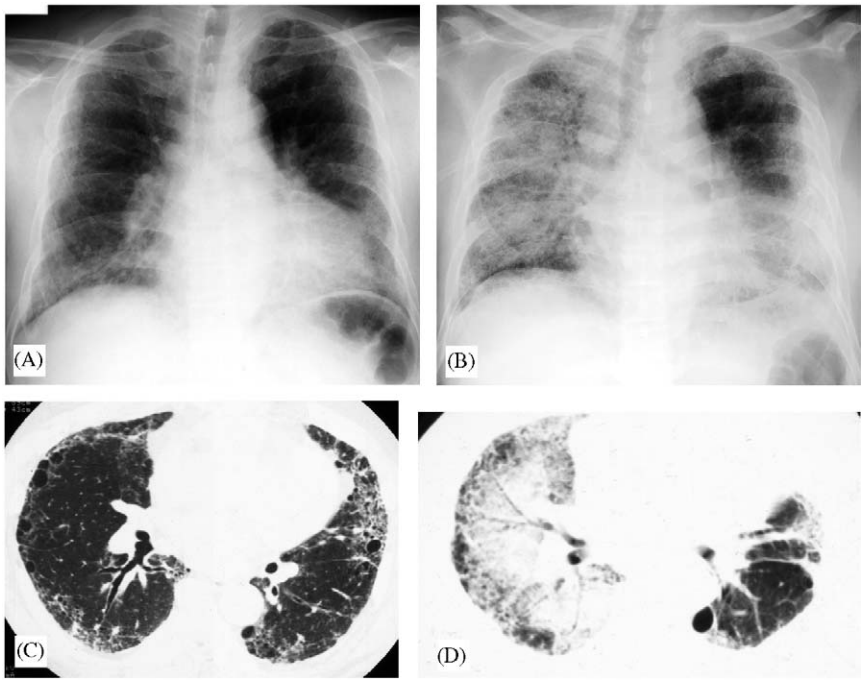

Figure 1 A 60-year-old man with IPF who underwent left-sided surgical biopsy. (A) Chest radiograph before surgical lung biopsy (SLB) shows predominantly peripheral, bilateral lower zone reticular shadows. (B) Chest radiograph obtained 5 days after SLB shows bilateral ground glass changes and consolidation, predominantly in the nonoperated lung. (C) CT scan of the lower lobes before surgical lung biopsy (SLB) shows peripheral bilateral reticular change. (D) CT scan of the lower lobes obtained 5 days after SLB shows enhanced ground glass change and consolidation affecting the nonoperated lung.

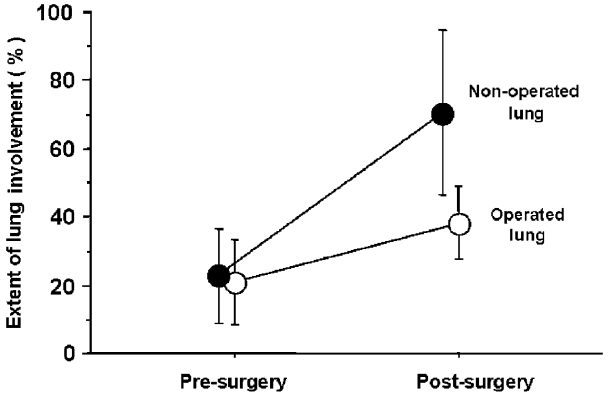

Figure 2 Quantification of extent of lung involvement pre- and postbiopsy in the operated and nonoperated lungs (filled circles, nonoperated lung; open circles, operated lung). Regions of significantly increased density were seen pre- and postoperatively in both the operated ($20.7 \pm 12.5\%$ versus $38.2 \pm 10.8\%$, $P = 0.0431$) and non-operated lung ($22.7 \pm 13.8\%$ versus $70.5 \pm 24.4\%$, $P = 0.0431$), but the extent of the elevation of the CT density was significantly greater on the nonoperated side ($P = 0.0251$).

even when the short-term course after operation is favorable.

In the present study, none of the patients with IPF who experienced acute exacerbation,[14,15] had an accelerated decline or subacute course before SLB. The outcome of acute exacerbation in IPF was poor: 2 of 3 patients died. Recently, Ultz et al. reported that 2 IPF/UIP patients died from ARDS or other respiratory failure within 30 days of surgical lung biopsy,[3] and we suspect that acute exacerbation occurred postoperatively in these patients. Special attention needs to be paid to the possibility of postsurgical acute exacerbation of IPF.

BALF findings for the nonoperated lung in 3 patients at the time of postbiopsy exacerbation showed a significant increase in neutrophil fraction compared with preoperative findings. Therefore, acute exacerbation after SLB may involve neutrophilic lung injury although it could simply reflect a widespread increase of capillary permeability.

It is worth noting that while in many cases infiltrates appeared in both the operated and nonoperated lung in this study, four of 5 cases showed more conspicuous abnormalities on the nonoperated side. This finding is compatible with the report of Padley et al., who demonstrated an asymmetric form of ARDS following pulmonary resection.[10] Thought must be given, therefore, to factors that can explain the contra-lateral exacerbation.

Table 3 Therapy and outcome of the five patients with post-biopsy acute exacerbation.

	Case 1	Case 2	Case 3	Case 4	Case 5
Histologic diagnosis	UIP	UIP	UIP	NSIP	OP
IPPV	+	+	—	+	—
NPPV	—	+	—	—	+
Corticosteroid	+	+	+	+	+
Pulse therapy	+	+	+	—	—
Two mg/kg/day followed by a tapered dosage	—	+	—	+	+
Immunosuppressant	+	+	—	—	+
Outcome	Died at 6 mo	Died at 1 mo	Alive at 78 mo	Alive at 62 mo	Alive at 38 mo

Definition of abbreviations: IPPV = invasive positive pressure ventilation, NPPV = noninvasive positive pressure ventilation, Pulse therapy = methylprednisolone 1 g/kg/day, for 3 days.

Compared with acute exacerbation following lung biopsy, ARDS following pneumonectomy or lobectomy for lung carcinoma has been well recognised.[5,9] High concentrations of inspired oxygen associated with single-lung ventilation or ischemic/reperfusion injury are thought to cause acute lung injury.[16,17] The technique of single-lung ventilation is performed in most surgical lung biopsies. During surgery, the contralateral lung remains ventilated and serves as the source of maintained patient oxygenation. If lung injury is caused at this time, the contralateral lung may be more adversely affected postoperatively. Because oxygenation is impaired during single-lung ventilation by the physiological shunt effect of the collapsed lung undergoing the biopsy procedure, a high concentration of inspired oxygen might have to be used. In some cases, a high airway pressure and tidal volume also might be used. In this regard, the patients in the present study who experienced postoperative exacerbation had received 100% oxygen ventilation for 40–170 min during surgery. Unfortunately intraoperative tidal volume could not be confirmed from anesthesia records. Because $PaCO_2$ was kept at nearly the normal range in blood gas during surgery, it would not be possible that tidal volume was limited.

In recent years, lung damage resulting from ventilator management (ventilator-induced lung injury; VILI) has been shown in animal experiments.[18] Ventilator associated lung injury (VALI) has also been demonstrated clinically.[19] Factors in VALI are presumed to include oxygen toxicity due to 100% oxygen inhalation[20] and increased tidal volume, and shear stress caused by repeated alveolar collapse and opening. Based on the foregoing, we speculated that the main cause of postoperative exacerbation is ventilator associated lung injury that was caused by intraoperative respiratory management.

The frequency of ALI and ARDS after lung resection has been reported to be related to the extent of resection; the highest frequency was observed after extensive resection (12.9%), followed by pneumonectomy (6.0%), lobectomy (3.7%), and minor resection (1.0%).[17] Accordingly, despite the lower surgical invasiveness of biopsy than in this study, the frequency of postoperative exacerbation following SLB was 2.1%. Further studies are needed to determine whether underling interstitial pneumonia enhances the risk of acute lung injury following pulmonary resection. It is also notable that 3/5 patients survived acute exacerbation. While numbers are too small to be definitive, this outcome appears better than that seen in spontaneous acute exacerbation and may reflect a response to corticosteroid therapy.

In summary, we report acute exacerbation following surgical lung biopsy in consecutive 236 patients with interstitial pneumonia. When surgical lung biopsy is performed in cases of interstitial pneumonia, it is important to be aware of the possibility of postoperative acute exacerbation, even after an apparently uneventful immediate postoperative course. After exclusion of other possible causes of deterioration, especially infection, this diagnosis should be considered and would then allow the early institution of corticosteroid therapy. While the present study was not designed to elucidate the cause, the asymmetric image findings suggest that intraoperative respiratory management is one possibility. This requires further study.

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